

WE CLAIM:

1. A process for the preparation of an optionally protected 1-halo-furanose comprising the steps of:
 - (a) reacting a furanose with an alcohol to form of an alkyl acetal;
 - 5 (b) optionally protecting the remaining free hydroxyls of the alkyl acetal of the furanose to form an optionally protected alkyl acetal the furanose; and then
 - (c) reacting the optionally protected alkyl acetal of the furanose with an acyl halide that generates an anhydrous acid halide *in situ* to form an
10 optionally protected 1-halo-furanose.
2. A process for the preparation of an optionally protected 1-halo-2-deoxyribose comprising the steps of:
 - (a) reacting a 2-deoxyribose with an alcohol to form of a 1-O-alkyl-2-deoxyribose;
 - 15 (b) optionally protecting the remaining free hydroxyls of the 1-O-alkyl-2-deoxyribose to form an optionally protected 1-O-alkyl-2-deoxyribose; and then
 - (c) reacting the optionally protected 1-O-alkyl-2-deoxyribose with an acyl
20 halide that generates an anhydrous acid halide *in situ* to form an optionally protected 1-halo-2-deoxyribose.
3. The process of claim 2, wherein the alkyl acetal of 2-deoxyribose is protected with aromatic esters.
4. The process of claim 3, wherein the alkyl acetal of 2-deoxyribose is protected with toluoyl groups.

5. The process of claim 2, wherein the alcohol of step (a) is methanol or ethanol to form a methyl or ethyl acetal.
6. The process of claim 2, wherein the alcohol of step (a) is methanol to form a methyl acetal.
- 5 7. The process of claim 6, wherein the acyl halide is acetyl chloride, to generate anhydrous HCl *in situ* to form an optionally protected 1-chloro-2-deoxyribose.
8. The process of claim 2, wherein the optionally protected 1-halo-2-deoxyribose is further coupled with a silylated base.
9. The process of claim 8, wherein the coupling reaction is performed in
10 chloroform.
10. The process of claim 8, wherein the silylated base is added in excess.
11. The process of claim 10, wherein the silylated base is added in a 2 molar excess.
12. The process of 8, wherein the silylated base is a silylated uracil or a silylated thymine.
- 15 13. A process for the preparation of an optionally protected β -L-2'-deoxythymidine comprising the steps of:
- (a) reacting a L-2-deoxyribose with an alcohol to form of a L-1-O-alkyl-2-deoxyribose;
- (b) optionally protecting the remaining free hydroxyls of the L-1-O-alkyl-2-deoxyribose to form an optionally protected L-1-O-alkyl-2-deoxyribose;
20
- (c) reacting the optionally protected L-1-O-alkyl-2-deoxyribose with an acyl halide that generates an anhydrous acid halide *in situ* to form an optionally protected L-1-halo-2-deoxyribose;
- (d) coupling the optionally protected L-1-halo-2-deoxyribose with silylated
25 thymine to form an optionally protected β -L-2'-deoxythymidine; and then

(e) deprotecting the optionally protected β -L-2'-deoxythymidine, if necessary, to obtain a β -L-2'-deoxythymidine.

14. The process of claim 13, wherein the coupling reaction is performed in chloroform.

15. The process of claim 13, wherein the silylated thymine is added in excess.

16. The process of claim 15, wherein the silylated thymine is added in a 2 molar excess.

17. A process for the preparation of an optionally protected β -L-2'-deoxyuridine comprising the steps of:

(a) reacting a L-2-deoxyribose with an alcohol to form of a L-1-O-alkyl-2-deoxyribose;

(b) optionally protecting the remaining free hydroxyls of the L-1-O-alkyl-2-deoxyribose to form an optionally protected L-1-O-alkyl-2-deoxyribose;

(c) reacting the optionally protected L-1-O-alkyl-2-deoxyribose with an acyl halide that generates an anhydrous acid halide *in situ* to form an optionally protected L-1-halo-2-deoxyribose;

(d) coupling the optionally protected L-1-halo-2-deoxyribose with silylated uracil to form an optionally protected β -L-2'-deoxyuridine; and then

(e) deprotecting the optionally protected β -L-2'-deoxyuridine, if necessary, to obtain a β -L-2'-deoxyuridine.

18. The process of claim 17, wherein the coupling reaction is performed in chloroform.

19. The process of claim 17, wherein the silylated uracil is added in excess.

20. The process of claim 19, wherein the silylated uracil is added in a 2 molar excess.

21. A process for the preparation of an optionally protected cytidine nucleoside comprising the steps of:

(a) reacting an optionally protected uridine nucleoside with a sulfonyl halide and ammonia to form an optionally protected cytidine nucleoside.

5 22. The process of claim 21, wherein the sulfonyl halide is tosyl chloride.

23. The process of claim 21, wherein the ammonia is liquid ammonia.

24. The process of claim 21, wherein the reaction is accomplished at room temperature.

10 25. The process of claim 21, wherein the optionally protected uridine nucleoside is an optionally protected β -L-2'-deoxyuridine to form an optionally protected β -L-2'-deoxycytidine.

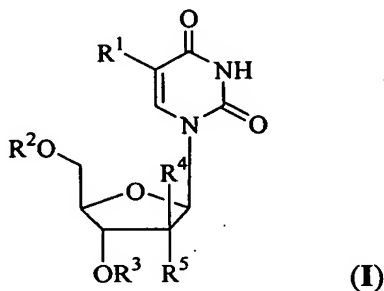
26. The process of claim 21, further comprising the step of separating the optionally protected cytidine nucleoside from the unreacted optionally protected uridine nucleoside.

15 27. The process of claim 26, wherein the separation is accomplished non-chromatographically.

28. The process of claim 26, wherein the separation is accomplished via extraction.

29. A process for the preparation of a β -(D or L)- or α -(D or L)-cytidine nucleoside comprising the steps of:

(a) preparing or obtaining a β -(D or L)- or α -(D or L)-uracil nucleoside of structure (I)



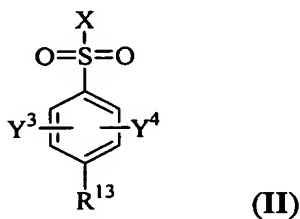
wherein

R^1 is a hydrogen atom, an alkyl group, a substituted alkyl group, a halogen atom, an alkoxyl group or a substituted alkoxy group;

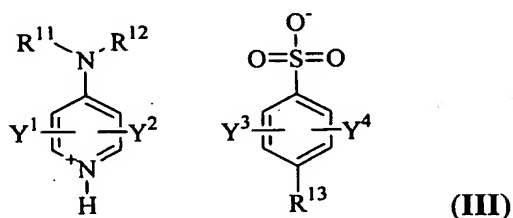
each R^2 and R^3 is independently hydrogen, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and

each R^4 and R^5 is independently a hydrogen atom, an alkyl group, a substituted alkyl group, a halogen atom, an alkoxyl group, a substituted alkoxyl group, or an acyloxyl group; and then

(b) activating the compound of structure (I) with a sulfonyl halide of structure (II)



optionally in the presence of a pyridinium salt of structure (III)



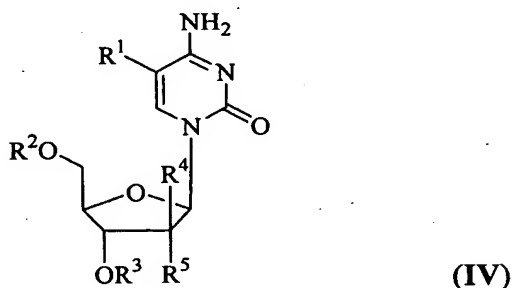
wherein

X is a halogen (F, Cl, Br, and I);

5 R^{11} , R^{12} and R^{13} are independently hydrogen, alkyl, alkenyl or alkynyl, though preferably a lower alkyl; and

Y^1 , Y^2 , Y^3 and Y^4 are independently hydrogen, halogen, alkyl, alkenyl or alkynyl, acyl, alkoxy or thioalkyl, though preferably hydrogen; and then

10 (c) reacting the activated compound with gaseous or liquid ammonia, to form a β -(D or L)- or α -(D or L)-cytidine of structure (IV)



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are defined above.

30. The process of claim 29, wherein R^1 , R^4 , and R^5 are H.

15 31. The process of claim 29, wherein R^1 is a methyl group; R^4 and R^5 are H; and R^2 is an amino acid residue.

32. The process of claim 31, wherein the amino acid residue is *L*-valyl.

33. The process of claim 29, wherein R^1 is a methyl group; R^4 and R^5 are H; and each R^2 and R^3 independently is an amino acid residue.

34. The process of claim 33, wherein the amino acid residue is *L*-valyl.

35. The process of claim 29, wherein the sulfonyl halide is tosyl chloride.

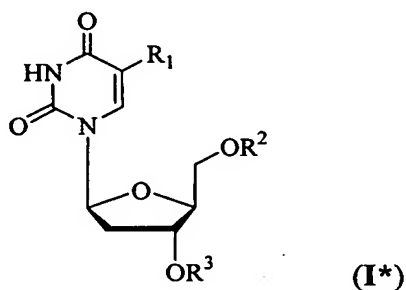
5 36. The process of claim 29, further comprising the step of separating the β -(D or L)- or α -(D or L)-cytidine nucleoside from the unreacted β -(D or L)- or α -(D or L)-uridine nucleoside.

37. The process of claim 36, wherein the separation is accomplished non-chromatographically.

10 38. The process of claim 36, wherein the separation is accomplished via extraction.

39. A process for the preparation of a β -L-2'-deoxy-cytidine comprising the steps of:

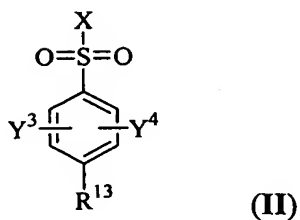
(a) preparing or obtaining a β -L-2'-deoxy-uridine of structure (I*)



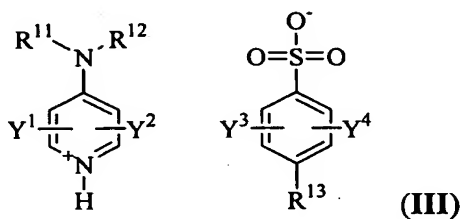
15 wherein R^2 and R^3 are independently hydrogen, acyl, silyl or a derivative of an amino acid; and

R^1 is hydrogen, halogen, alkyl, alkenyl or alkynyl, acyl, amine, alkylamine, aminoalkyl, hydroxyl, alkoxy, oxyalkyl, thiol, thioalkyl or alkylmercaptan; and then

(b) activating the compound of structure (I*) with a sulfonyl halide of structure (II)



optionally in the presence of a pyridinium salt of structure (III)



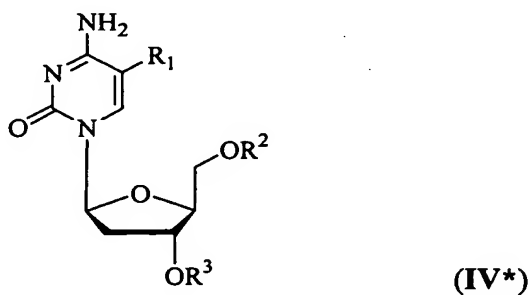
wherein

X is a halogen (F, Cl, Br, and I);

R¹¹, R¹² and R¹³ are independently hydrogen, alkyl, alkenyl or alkynyl, though preferably a lower alkyl; and

Y¹, Y², Y³ and Y⁴ are independently hydrogen, halogen, alkyl, alkenyl or alkynyl, acyl, alkoxy or thioalkyl, though preferably hydrogen; and then

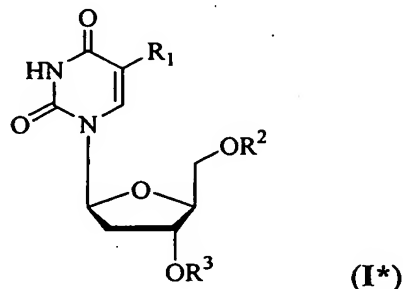
(c) reacting the activated compound with gaseous or liquid ammonia, to form a β-L-2'-deoxy-cytidine of structure (IV*)



wherein R¹, R² and R³ are defined above.

40. The process of claim 39, wherein R¹ is H.
41. The process of claim 39, wherein R¹ is H; and R² is an amino acid residue.
42. The process of claim 42, wherein the amino acid residue is *L*-valyl.
- 5 43. The process of claim 39, wherein R¹ is H; and each R² and R³ independently is an amino acid residue.
44. The process of claim 43, wherein the amino acid residue is *L*-valyl.
45. The process of claim 39, wherein the sulfonyl halide is tosyl chloride.
46. The process of claim 39, further comprising the step of separating the desired β-L-2'-deoxy-cytidine from unreacted β-L-2'-deoxyuridine.
- 10 47. The process of claim 46, wherein the separation is accomplished non-chromatographically.
48. The process of claim 46, wherein the separation is accomplished via extraction.
49. A process for the preparation of a β-L-2'-deoxy-cytidine comprising the steps of:
- 15 (a) reacting a L-2-deoxyribose with an alcohol to form of a L-1-O-alkyl-2-deoxyribose;
- (b) optionally protecting the remaining free hydroxyls of the L-1-O-alkyl-2-deoxyribose to form an optionally protected L-1-O-alkyl-2-deoxyribose;
- (c) reacting the optionally protected L-1-O-alkyl-2-deoxyribose with an acyl
- 20 halide that generates an anhydrous acid halide *in situ* to form an optionally protected L-1-halo-2-deoxyribose;

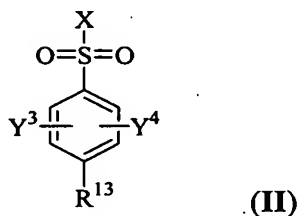
(d) coupling the optionally protected L-1-halo-2-deoxyribose with silylated uracil to form an optionally protected β -L-2'-deoxyuridine of structure (I*)



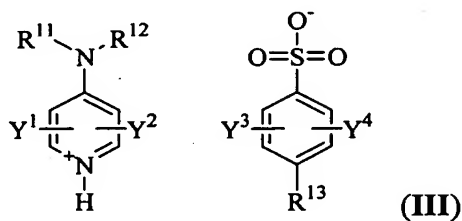
wherein R^2 and R^3 are independently hydrogen, acyl, silyl or a derivative of an amino acid; and

R^1 is hydrogen, halogen, alkyl, alkenyl or alkynyl, acyl, amine, alkylamine, aminoalkyl, hydroxyl, alkoxy, oxyalkyl, thiol, thioalkyl or alkylmercaptan; and then

(e) activating the compound of structure (I*) with a sulfonyl halide of structure (II)



optionally in the presence of a pyridinium salt of structure (III)



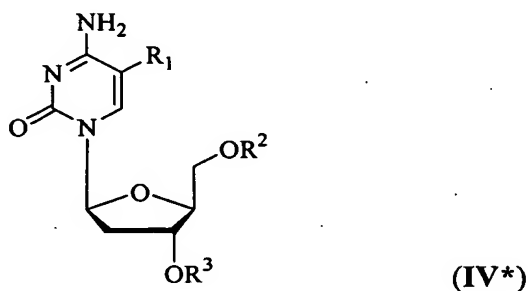
wherein

X is a halogen (F, Cl, Br, and I);

R^{11} , R^{12} and R^{13} are independently hydrogen, alkyl, alkenyl or alkynyl, though preferably a lower alkyl; and

Y^1 , Y^2 , Y^3 and Y^4 are independently hydrogen, halogen, alkyl, alkenyl or alkynyl, acyl, alkoxy or thioalkyl, though preferably hydrogen; and then

(f) reacting the activated compound with an amine, such as gaseous or liquid ammonia, to form a β -L-2'-deoxy-cytidine of structure (IV*)



wherein R^1 , R^2 and R^3 are defined above.

- 10 50. The process of claim 49, wherein the L-1-O-alkyl-2-deoxyribose is protected with aromatic esters.
51. The process of claim 50, wherein the L-1-O-alkyl-2-deoxyribose is protected with toluoyl groups.
- 15 52. The process of claim 49, wherein the alcohol of step (a) is methanol or ethanol to form a L-1-O-(methyl or ethyl)-2-deoxyribose.
53. The process of claim 49, wherein the alcohol of step (a) is methanol to form a L-1-O-methyl-2-deoxyribose.
54. The process of claim 49, wherein the acyl halide is acetyl chloride, to generate anhydrous HCl *in situ* to form an optionally protected 1-chloro-2-deoxyribose.
- 20 55. The process of claim 49, wherein the coupling reaction is performed in chloroform.
56. The process of claim 49, wherein the silylated base is added in excess.

57. The process of claim 56, wherein the silylated base is added in a 2 molar excess.

58. The process of claim 49, wherein R¹ is H.

59. The process of claim 49, wherein R¹ is H; and R² is an amino acid residue.

60. The process of claim 59, wherein the amino acid residue is *L*-valyl.

61. The process of claim 49, wherein R¹ is H; and each R² and R³ independently is an amino acid residue.

62. The process of claim 61, wherein the amino acid residue is *L*-valyl.

63. The process of claim 49, wherein the sulfonyl halide is tosyl chloride.

64. The process of claim 49, further comprising the step of separating the desired β -L-2'-deoxy-cytidine from the unreacted optionally protected β -L-2'-deoxyuridine.

65. The process of claim 64, wherein the separation is accomplished non-chromatographically.

66. The process of claim 64, wherein the separation is accomplished via extraction.

67. A process for the preparation of an optionally protected β -L-2'-deoxycytidine comprising the steps of:

(a) aminating an optionally protected β -L-2'-deoxyuridine to obtain an optionally protected β -L-2'-deoxycytidine; and then

(b) non-chromatographically separating the optionally protected β -L-2'-deoxycytidine from the optionally protected β -L-2'-deoxyuridine.

68. The process of claim 58, wherein the separation is accomplished via extraction.